REMARKS

Claim Objections

The Examiner objects to claim 19 under 37 CFR § 1.75(c) as being in improper form because a multiple dependent claim cannot depend from two sets of claims for different features. Applicants amend claim 19 to incorporate the compounds recited in claim 9 into that claim. Applicants respectfully submit that this amendment obviates the Examiner's objection of claim 19 and respectfully requests that the Examiner withdraw his rejection of that claim.

Claim Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 12-17 and 20 under 35 U.S.C. § 112, first paragraph and although he acknowledges that the claims are enabled for the treatment of stroke, he asserts that there is a lack of enablement for the treatment of diseases, other than stroke, encompassed by those claims. This rejection is respectfully traversed and reconsideration thereof is respectfully requested. Applicants respectfully submit that in light of the cancellation of claims 13-15 this rejection of claims 13-15 is rendered moot. Thus, the following remarks in response to this rejection relate to claims 12, 16, 17, and 20.

Applicants amend claim 12 to delete reference to a method of inhibiting GSK-3 activity in "a patient in need thereof." Thus, amended claim 12 relates to a method of inhibiting GSK-3 in a biological sample. Applicants respectfully submit that this amendment to claim 12 is supported by the specification at paragraph [0086] which sets forth the method of inhibiting GSK-3 in a biological sample. Applicants respectfully submit that this amendment of claim 12 obviates the Examiner's rejection of that claim under 35 U.S.C. § 112, first paragraph and respectfully request that the Examiner withdraw his rejection of claim 12.

Applicants respectfully submit that the connection between GSK-3 and the diseases set forth in claims 16 and 17 was well established in the art at the time of filing. Furthermore, the Hardt reference cited by the Examiner to support his assertion that "[t]he state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity" actually provides a clear nexus between inhibition of GSK-3 and the diseases recited in these claims. Specifically, the Hardt reference, entitled "Glycogen Synthase Kinase-3β A Novel Regulator of Cardiac Hypertrophy and Development" describes the role of GSK-3 in *cardiac hypertrophy*. Although, as the Examiner asserts, this reference does indicate that there are many unanswered questions regarding the GSK-3 function *with respect to cardiac hypertrophy*, this reference also describes the well known association of GSK-3 with the diseases set forth in claims 16 and 17. In particular, the author states that "[a]lthough GSK-3β was initially described for its function to inhibit glycogen synthesis through phosphorylation of glycogen synthase, it has been revealed that GSK-3β **regulates a wide range of cellular functions, including metabolism, gene expression, and cytoskeletal integrity**. GSK-3β is also involved in a **variety of disease processes,** such as tumirogenesis and the **development of Alzheimer's disease**." See Hardt, et al., page 1055, ¶ 2 (emphasis added). Moreover, that same reference clearly indicates that GSK-3 is a ubiquitously expressed kinase that is involved in numerous biochemical pathways. Accordingly, Applicants respectfully submit that the claims are indeed enabled for the diseases claimed therein.

The Examiner cites the Cecil Textbook of Medicine, 20th edition (1996) which states that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease." Applicants respectfully submit that since the publication of this reference in *1996*, the FDA approved the drug Aricept®, among others, specifically for the treatment of Alzheimer's disease. Furthermore, recent advances in the kinase art, as described by Hardt, et al., and others, directly link GSK-3 with various neurodegenerative disorders including Alzheimer's disease.

The Examiner asserts that the disclosure does not provide how the reported *in vitro* data correlates to the treatment of the assorted list of disorders of the instant claims. In addition, the Examiner states that factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. Applicants respectfully traverse. First, applicants respectfully submit that working examples are not required by U.S.C. § 112, first paragraph. See MPEP § 2164.02. Also,

Applicants would like to point out that the MPEP states that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate." See MPEP § 2164.02. Because the models cited in the background section of the present application do correlate the inhibition of GKS-3 with the diseases recited by the instant claims, those claims are indeed enabled. Specifically, description of these correlating models is found generally at paragraphs 7 through 11. Furthermore, and as discussed in detail above, the Hardt reference cited by the Examiner provides additional correlation between GSK-3 and the diseases recited in the instant claims. Moreover, the court in *In re Brana*, 52 F.3d 1560 (Fed. Cir. 1995) reversed the PTO decision that *in vitro* data did not support *in vivo* applications. Only a "reasonable correlation" is required, and the test does not have to be "highly predictive" as the Examiner suggests. Additionally, Applicants would like to point out that each of the rejected claims recites *treating or lessening the severity* of certain diseases, or conditions, and does not recite the *reversal* of diseases such that a "magic bullet" is within the scope of the instant claims.

Enablement requires the applicant to provide sufficient guidance so that one of skill in the art may use the invention. The MPEP states that "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." See MPEP § 2164.06. Applicants do in fact provide the tools to make the compounds of the instant invention and assess the activity of those compounds. And, in light of *Brana* and the various sections of the MPEP cited herein, the *in vitro* data and methods do support the *in vivo* applications of the instant claims. Thus, applicants respectfully submit the above arguments and request that the Examiner acknowledge sufficient enablement of claims 16 and 17.

In light of the cancellation of claims 13-15, Applicants amend claims 19 and 20 to depend from claims 16-18. Although claim 19 stands objected to, and was not considered by the Examiner on its merits, Applicants respectfully submit that amended claims 19 and 20 are patentable and respectfully request acknowledgment of the same.

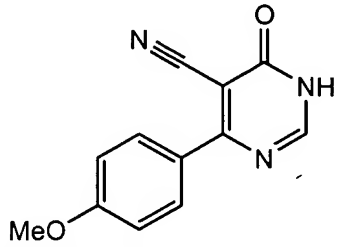
Accordingly, in light of the arguments set forth above, Applicants respectfully submit that claims 16, 17, and 20 are indeed enabled and request acknowledgment thereof. Thus, Applicants respectfully request that the Examiner withdraw his rejection of claims 16, 17, and 20 under 35 U.S.C. § 112, first paragraph.

Claim Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejects claim 11 under 35 U.S.C. § 112, second paragraph as being indefinite because the term "composition" lacks antecedent basis. Specifically, claim 11 directed to a "composition" depends from claim 9 which is directed to a "compound". As suggested by the Examiner, Applicants amend claims 11 to depend from composition claim 10 to correct this inadvertent error. Applicants respectfully submit that this amendment of claim 11 obviates the Examiner's rejection of this claim and respectfully request acknowledgment of the same.

Claim Rejections under 35 U.S.C. § 102(b)

Claims 1, 2, 4, 5, 9, and 10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Abdel-Megid, et al. Specifically, the compound of Abdel-Megid has the following structure:



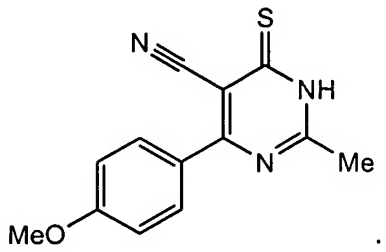
and corresponds to a compound of Applicants' claim 1 when W is oxygen and ring A is a 6-membered aryl ring (phenyl) substituted with one $-OR^1$ group wherein R^1 is aliphatic (methyl).

In order to expedite prosecution, Applicants amend claim 1 such that the rejection made under 35 U.S.C. § 102(b) as being anticipated by the compound of Abdel-Megid is obviated. Specifically, Applicants amend claim 1 such that R^1 cannot be $-OR^1$. Applicants respectfully submit that this amendment obviates the rejection of claim 1 under 35 U.S.C. § 102(b). Accordingly, Applicants respectfully request that the rejection of claim 1 under 35 U.S.C. § 102(b) be withdrawn. In light of the amendment to claim 1 obviating the rejection of that claim under 35 U.S.C. § 102(b), Applicants respectfully submit that claims dependent therefrom are rendered patentable by that amendment.

Claims 1, 2, 4, 5, and 10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Mittelbach, et al. Applicants respectfully submit that the amendments to claim 1, as described herein, renders moot any rejection under 35 U.S.C. § 102(b), as being anticipated by Mittelbach, et al. Accordingly, Applicants respectfully request that the rejection of claims 1, 2, 4, 5 and 10 as being anticipated by Mittelbach, et al., under 35 U.S.C. § 102(b) be withdrawn.

Claim Rejections under 35 U.S.C. § 103

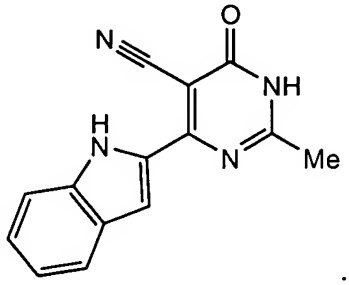
Claims 1, 3, 4, 5, 9, 10, and 11 are rejected under 35 U.S.C. § 103 as being unpatentable over Abdel-Megid, et al., CAPLUS Abstract 133:30702 (2000). The Abdel-Megid reference discloses the following compound:



This reference compound differs from the compounds of claim 1 in that the reference compound has a methyl substituent at the 2-position whereas claimed compounds are unsubstituted at the 2-position.

Claims 1, 2, 6, 9, 10, and 11 are rejected under 35 U.S.C. § 103 as being unpatentable over Kobayashi, et al., CAPLUS Abstract 88:31980 (1978).

The Kobayashi reference discloses the following compound:



This reference compound differs from the compounds of claim 1 in that the reference compound has a methyl substituent at the 2-position whereas claimed compounds are unsubstituted at the 2-position.

With respect to both rejections, the Examiner asserts that "the instantly claimed compounds differ from the reference compounds by a $-CH_2-$ group and it is well established that compounds that differ by a $-CH_2-$ group are structural homologs." In addition, the Examiner relies on *In re Hass*, 141 F.2d 122 (CCPA 1944) and *In re Henze*, 85 USPW 261 (CCPA 1950) to support his assertion that "compounds that are structurally homologous to prior art compounds are *prima facie* obvious" and that such compounds "are expected to possess similar properties." This rejection is respectfully traversed and reconsideration thereof is respectfully requested.

First, Applicants respectfully point out to the Examiner that the present compounds are not homologs of the reference compounds and differ from the reference compounds in regard to the *presence of a substituent as compared to the absence of that substituent* on the reference compound. Second, Applicants respectfully point out to the Examiner that *In re Henze* was overruled in *In re Stemniski*, 444 F.2d 581 (CCPA 1971) which held that "[a] discovery of an unexpected utility for a novel compound is evidence directly relevant to the issue of the unobviousness of the compounds claimed over those of the prior art." See *Stemniski*, at 584. In addition, Applicants respectfully point out that *In re Hass*, 141 F.2d 122 (CCPA 1944) is also not applicable in this case. Specifically, *In re Hass* related to the issue of whether a proper Markush group may exclude a homolog. Third, Applicants respectfully submit that the presently claimed compounds do have an unexpected activity over the Abdel-Medig and Kobayashi compounds, as discussed in detail with respect to the expectation of success, *infra*. Thus, the present compounds are not "*prima facie* obvious" for being homologs, as suggested by the Examiner.

Applicants respectfully point out that as recited in the MPEP § 2143, "to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation ... to modify the reference ... Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations." For the reasons set forth below, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness.

First, Applicants respectfully submit that the Examiner has failed to show that the references teach or suggest all of the claim limitations, as required to support a *prima facie* case of obviousness. Specifically, the references do not teach nor suggest compounds that are unsubstituted at the 2-position as recited by amended claim 1 of the present application.

Second, Applicants respectfully submit that the Examiner has not established that there exists the required reasonable expectation of success within the references. The teachings, suggestions, and expectation of success must come from the prior art, not applicants' disclosure. See *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants respectfully submit that the cited references provide no reasonable expectation of success and, in fact, teach away form Applicants' claimed invention.

Specifically, and as noted by the Examiner, the Abdel-Megid reference clearly teaches away from Applicants' claimed invention because the document indicate that the compounds are

useful only as a co-enzyme factor in the acceleration of cellobiase activity. Similarly, the Kobayashi reference clearly teaches away from Applicants' claimed invention because the document indicate that the compounds are useful only as having some antitumor effect against a solid type of Ehrlich carcinoma. Moreover, the Kobayashi abstract indicates that the single compound, depicted above, "was found to have *some* antitumor effect, but *no other derivs. were found effective.*" (Emphasis added). The Federal Circuit has held that "[w]here the prior art does not teach the utility asserted for the claimed compounds, the expectation may not arise, and the motivation would dissipate." See *In re Lalu*, 747 F.2d 703, 707 (Fed. Cir. 1984). In the present case, the references provide no reasonable expectation of success that any of the compounds disclosed therein would be useful as GSK-3 inhibitors, and thus do not establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully submit that amended claims 1 and 9, and dependent claims 2-6, 9, 10, and 11, are patentable over the disclosure of Abdel-Megid, et al., and respectfully request that the Examiner withdraw his rejection of these claims under 35 U.S.C. § 103.

Miscellaneous Amendments

Applicants amend claim 7 to independent form and incorporate the limitations of claim 1 from which claim 7 formerly depended.

Claim 6 is amended to remove multiple dependency. Specifically, Claim 6 is amended to depend from claim 21.

Claim 8 is amended to depend from claim 21 rather than amended claim 6.

In light of the amendments to claims 1, 7 and 9, as described herein, claim 10 is amended to be multiply dependent on claim 1, 7 or 9.

Claims 1, 12, and 16-18 are amended to correct an inadvertent typographical error within the definition of R^2.

Applicants add new claims 21 and 22. Support for claim 21 is found in original claim 1. Support for claim 22 is found in Table 1 of the specification at pages 13-20. Specifically, each ring A group depicted in new claim 22 is found in Table 1.

No new matter has been added.

Applicants respectfully submit the above amendments and arguments and respectfully request that the Examiner acknowledge patentability of pending claims 1-12, 16-20 and new claims 21 and 22. Applicants invite the Examiner to call their agent, Andrea L. C. Robidoux, at

(617) 248-5124 with any questions pertaining to the above-identified application in order to expedite prosecution of this case.

Respectfully submitted,

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